Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.
Vol. 62, No. 1, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.02.070

EDITORIAL COMMENT

Chronic Exercise

A Contributing Factor to Atrial Fibrillation?*

Xander H. T. Wehrens, MD, PhD,
David Y. Chiang, BS, Na Li, PhD
Houston, Texas

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in the clinical setting (1). In the general population, the prevalence of AF increases with age, ranging from 0.5% in patients younger than 40 years to 5% in patients older than 65 years (2). Less is known about the prevalence in athletes, with several epidemiological studies reporting different findings due to variations in age, years of training, and associated comorbidities. What is known, however, is that athletes are prone to arrhythmias, and AF is the most common arrhythmia in the athletic population.

See page 68

A number of studies have described that vigorous endurance exercise, such as marathon running (3), cross-country skiing (4), and cycling (5), increases the risk of AF in humans. There are only a limited number of studies to date that have investigated the epidemiology of AF in athletes. Moreover, the mechanisms underlying AF development in athletes are not well defined.

A number of studies have shed light on possible causes of AF in athletes such as structural remodeling, autonomic nervous system alterations, hypovolemia, and illicit drug use, as reviewed previously (2). Because of their endurance training, athletes may experience a chronic increase in atrial pressure. Elevated atrial pressure by itself can lead to atrial dilation, shortening of the atrial effective refractory period, and increased AF inducibility in the isolated Langendorff perfused rabbit hearts (6). Conversely, one clinical study found that while the left atrium was enlarged in a population of athletes, the incidence of AF and other supraventricular tachyarrhythmias was not increased (7). Besides enlargement, chronic inflammation leading to atrial fibrosis has also been proposed as a cause of AF in athletes (8,9). This concept is supported by the observation of acute elevated inflammatory markers such as C-reactive protein in response to exercise (10). A recent study in exercised rats also revealed enhanced cardiac fibrosis and an increased arrhythmia inducibility (11).

In addition to structural remodeling, alteration in the activity of the autonomic nervous system may potentially contribute to AF in athletes. One study in dogs infused with catecholamines and/or acetylcholine suggests that cholinergic or vagal stimulation is mainly responsible for spontaneous AF initiation whereas adrenergic stimulation modulates the initiation as well as the maintenance of AF (12). This finding is supported by an older study, in which vagal stimulation induced AF in dogs (13). This study also showed that vagal stimulation necessary re-entry circuits by shortening the atrial refractory period (13). In humans, the GIRAFA (Grup Integrat de Recerca en Fibril-lació Auricular) study found that vagal AF, or AF activated by the parasympathetic nervous system, is the main form of lone AF; this study, however, was not conducted in athletes (14). Swanson (9) offered the provocative hypothesis that esophageal acid reflux caused by exercise could stimulate the vagal nerves (due to the proximity to the esophagus), thus leading to AF in athletes. Finally, two other more extrinsic mechanisms have been suggested to either induce or contribute to AF in athletes. First, if inappropriately hydrated, athletes may suffer from dehydration or hypovolemia, both of which have been proposed in a case series to cause AF (15). However, all patients in that particular patient cohort were critically ill, which questions the validity of these findings to all athlete subgroups. Second, several illicit drugs or substances banned by the World Anti-Doping Agency may cause cardiac arrhythmias, including AF in athletes (16). These drugs include anabolic steroids, erythropoiesis-stimulating agents, growth hormone, and stimulants (2). However, more studies are needed to elucidate the molecular pathways responsible for AF induction and maintenance in these cases.

In this issue of the *Journal*, Guasch et al. (17) have gone a step further to establish and characterize a novel animal model of endurance exercise. The authors focused on exploring the mechanisms underlying AF development related to chronic endurance training. Based on previous studies (11), the authors subjected rats to daily 1-hour treadmill training for 8 or 16 weeks, which mimicked chronic endurance exercise in athletes. Based on maximum oxygen uptake, the authors suggested that the 16-week treadmill-training regimen in rats corresponds roughly to about 10 years of exercise training in humans. Next, the authors demonstrated that the rats subjected to chronic exercise were more susceptible to pacing-induced AF. Furthermore, the increase in AF susceptibility was associated with an enhanced

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Cardiovascular Research Institute, Department of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, Texas. This study was supported by the American Heart Association South Central Affiliate 09POST2260300 and 12BGIA12050207 (to Dr. Li), predoctoral fellowship 12PRE11700012 (to Mr. Chiang), the National Heart, Lung, and Blood Institute (R01-HL089598 and R01-HL091947), and the Leducq Foundation (to Dr. Wehrens).

vagal tone, atrial dilation, and increased fibrosis, similar to findings in humans with long-term endurance training (18). In addition, the authors showed that the cessation of exercise reversed AF inducibility in these animals, suggesting a cause-and-effect relationship between endurance exercise and AF promotion. However, this deconditioning protocol failed to attenuate atrial dilation and fibrosis, suggesting that molecular pathways other than structural remodeling also contribute to the AF arrhythmogenesis in athletes. Consistent with this notion, the authors demonstrated that an enhanced baroreflex and sensitivity to cholinergic stimulation of the acetylcholine-dependent potassium current (I_{KACh}) play central roles in this exercise model. Furthermore, molecular studies suggested that altered messenger ribonucleic acid expression levels of several regulators of G-protein–signaling (RGS) proteins may contribute to the augmentation of I_{KACh} sensitivity to vagal tone. To further support this notion, the authors used a mouse model that lacks the RGS4 protein, mimicking the situation in the animal model, and demonstrated that RGS4 deficiency predisposes to pacing-induced AF.

This work by Guasch et al. (17) is the first study to date that provides mechanistic insights into the pathogenesis underlying AF caused by chronic vigorous exercise. Their findings suggest that enhanced vagal activity plays an important role, through an augmented baroreflex responsiveness and increased sensitivity to cholinergic stimulation at the level of the atrial cardiomyocytes. As with every excellent innovative study, the current work raises several important questions. First, optical mapping experiments are needed in both animal models and in patients to determine the exact arrhythmic mechanism in response to endurance training. Second, it remains to be established whether other modes of high-intensity endurance training such as swimming and voluntary wheel-running involve similar pathogenic mechanisms associated with AF promotion. Third, other studies have suggested that endurance training could also modify intracellular calcium handling (19,20). A number of studies from Dr. Wisloff's group demonstrated that exercise training enhanced calcium cycling, through increasing the activity of calcium/calmodulin-dependent kinase IIδ (CaMKIIδ) (19,20). CaMKIIδ activity was also found to be enhanced in patients with AF (21) and associated with AF promotion through phosphorylation of its downstream targets, ryanodine receptor type 2 channels and phospholamban (22). We have demonstrated that the augmented CaMKII-mediated phosphorylation of ryanodine receptor type 2 channels promotes AF initiation by amplifying calcium release from the sarcoplasmic reticulum and ultimately increasing triggered activity by activation of the sodium/calcium exchanger (22). Therefore, it is intriguing to explore the possible mechanism of exercise-induced calcium remodeling associated with AF pathogenesis. Finally, although detraining might be beneficial in athletes, it remains to be determined which aspects of detraining are most beneficial in terms of reducing the risk of cardiac arrhythmias.

It seems reasonable to propose I_{KACh} blockers as a promising approach to AF prevention in athletes prone to this condition, given that selective I_{KACh} blockers are currently being developed for the treatment of AF because of their atrial-specific channel inhibition (23). Because atrial myocytes from athletes have a higher I_{KACh} sensitivity, selective I_{KACh} blockers might be less likely to reduce the already lower heart rates in athletes compared with similar drug classes such as muscarinic acetylcholine receptor antagonists. Guasch et al. (17) opens up new research avenues for both clinical and basic scientists to better understand the development and potential treatment of arrhythmias in athletes.

Reprint requests and correspondence: Dr. Xander H. T. Wehrens, Baylor College of Medicine, Molecular Physiology and Biophysics, One Baylor Plaza, BCM335, Houston, Texas 77030. E-mail: wehrens@bcm.edu.

REFERENCES

1. Kannel WB, Benjamin EJ. Current perceptions of the epidemiology of atrial fibrillation. Cardiol Clin 2009;27:13–24, vii.
2. Turagam MK, Velagapudi P, Kocheril AG. Atrial fibrillation in athletes. Am J Cardiol 2012;109:296–302.
3. Molina L, Mont L, Marrugat J, et al. Long-term endurance sport practice increases the incidence of lone atrial fibrillation in men: a follow-up study. Europace 2008;10:618–23.
4. Grimsmo J, Grundvold I, Maehlum S, Arnesen H. High prevalence of atrial fibrillation in long-term endurance cross-country skiers: echocardiographic findings and possible predictors—a 28-30 years follow-up study. Eur J Cardiovasc Prev Rehabil 2010;17:100–5.
5. Baldesberger S, Bauersfeld U, Candinas R, et al. Sinus node disease and arrhythmias in the long-term follow-up of former professional cyclists. Eur Heart J 2008;29:71–8.
6. Ravelli F, Allessie M. Effects of atrial dilatation on refractory period and vulnerability to atrial fibrillation in the isolated Langendorff-perfused rabbit heart. Circulation 1997;96:1686–95.
7. Pelliccia A, Maron BJ, Di Paolo FM, et al. Prevalence and clinical significance of left atrial remodeling in competitive athletes. J Am Coll Cardiol 2005;46:690–6.
8. Lindsay MM, Dunn FG. Biochemical evidence of myocardial fibrosis in veteran endurance athletes. Br J Sports Med 2007;41:447–52.
9. Swanson DR. Running, esophageal acid reflux, and atrial fibrillation: a chain of events linked by evidence from separate medical literatures. Med Hypotheses 2008;71:178–85.
10. Kasapis C, Thompson PD. The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. J Am Coll Cardiol 2005;45:1563–9.
11. Benito B, Gay-Jordi G, Serrano-Mollar A, et al. Cardiac arrhythmogenic remodeling in a rat model of long-term intensive exercise training. Circulation 2011;123:13–22.
12. Sharifov OF, Fedorov VV, Beloshapko GG, Glukhov AV, Yushmanova AV, Rosenshtraukh LV. Roles of adrenergic and cholinergic stimulation in spontaneous atrial fibrillation in dogs. J Am Coll Cardiol 2004;43:483–90.
13. Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. Am Heart J 1959;58:59–70.
14. Mont L, Tamborero D, Elosua R, et al. Physical activity, height, and left atrial size are independent risk factors for lone atrial fibrillation in middle-aged healthy individuals. Europace 2008;10:15–20.
15. Edwards JD, Wilkins RG. Atrial fibrillation precipitated by acute hypovolaemia. Br Med J (Clin Res Ed) 1987;294:283–4.
16. Furlanello F, Serdoz LV, Cappato R, De Ambroggi L. Illicit drugs and cardiac arrhythmias in athletes. Eur J Cardiovasc Prev Rehabil 2007;14:487–94.

17. Guasch E, Benito B, Qi X, et al. Atrial fibrillation promotion by endurance exercise: demonstration and mechanistic exploration in an animal model. J Am Coll Cardiol 2013;61:67–77.
18. Aizer A, Gaziano JM, Cook NR, Manson JE, Buring JE, Albert CM. Relation of vigorous exercise to risk of atrial fibrillation. Am J Cardiol 2009;103:1572–7.
19. Kemi OJ, Ellingsen O, Ceci M, et al. Aerobic interval training enhances cardiomyocyte contractility and Ca2+ cycling by phosphorylation of CaMKII and Thr-17 of phospholamban. J Mol Cell Cardiol 2007;43:354–61.
20. Kemi OJ, Ceci M, Condorelli G, Smith GL, Wisloff U. Myocardial sarcoplasmic reticulum Ca2+ ATPase function is increased by aerobic interval training. Eur J Cardiovasc Prev Rehabil 2008;15:145–8.
21. Voigt N, Li N, Wang Q, et al. Enhanced sarcoplasmic reticulum Ca2+ leak and increased Na+-Ca2+ exchanger function underlie delayed afterdepolarizations in patients with chronic atrial fibrillation. Circulation 2012;125:2059–70.
22. Chelu MG, Sarma S, Sood S, et al. Calmodulin kinase II-mediated sarcoplasmic reticulum Ca2+ leak promotes atrial fibrillation in mice. J Clin Invest 2009;119:1940–51.
23. Dobrev D, Carlsson L, Nattel S. Novel molecular targets for atrial fibrillation therapy. Nat Rev Drug Discov 2012;11:275–91.

Key Words: arrhythmia mechanisms ■ exercise training ■ ion currents ■ potassium channel.